Appendix 14

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Decline in Invasive Pneumococcal Disease after the Introduction of Protein–Polysaccharide Conjugate Vaccine

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ABSTRACT

BACKGROUND

In early 2000, a protein–polysaccharide conjugate vaccine targeting seven pneumococcal serotypes was licensed in the United States for use in young children.

METHODS

We examined population-based data from the Active Bacterial Core Surveillance of the Centers for Disease Control and Prevention to evaluate changes in the burden of invasive disease, defined by isolation of *Streptococcus pneumoniae* from a normally sterile site. Serotyping and susceptibility testing of isolates were performed. We assessed trends using data from seven geographic areas with continuous participation from 1998 through 2001 (population, 16 million).

RESULTS

The rate of invasive disease dropped from an average of 24.3 cases per 100,000 persons in 1998 and 1999 to 17.3 per 100,000 in 2001. The largest decline was in children under two years of age. In this group, the rate of disease was 69 percent lower in 2001 than the base-line rate (59.0 cases per 100,000 vs. 188.0 per 100,000, P<0.001); the rate of disease caused by vaccine and vaccine-related serotypes declined by 78 percent (P<0.001) and 50 percent (P<0.001), respectively. Disease rates also fell for adults; as compared with base line, the rate of disease in 2001 was 32 percent lower for adults 20 to 39 years of age (7.6 cases per 100,000 vs. 11.2 per 100,000, P<0.001), 8 percent lower for those 40 to 64 years of age (19.7 per 100,000 vs. 21.5 per 100,000, P=0.03), and 18 percent lower for those 65 years of age or more (49.5 per 100,000 vs. 60.1 per 100,000, P<0.001). The rate of disease caused by strains that were not susceptible to penicillin was 35 percent lower in 2001 than in 1999 (4.1 cases per 100,000 vs. 6.3 per 100,000, P<0.001).

CONCLUSIONS

The use of the pneumococcal conjugate vaccine is preventing disease in young children, for whom the vaccine is indicated, and may be reducing the rate of disease in adults. The vaccine provides an effective new tool for reducing disease caused by drug-resistant strains.

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In early 2000, a 7-valent protein–polysaccharide pneumococcal conjugate vaccine (Prevnar, Wyeth Lederle Vaccines) was licensed for use in infants and young children in the United States. This was the first vaccine that promised efficacy against pneumococcal disease for this high-risk group. In the second half of 2000, recommendations for routine use of the vaccine in all infants and children under two years of age and in high-risk children two through four years of age were published,[1,2] and distribution of the vaccine through public programs began. By August 2001, a shortage was reported.[3]

Controlled clinical trials have shown that the vaccine, when given as a four-dose regimen to infants, is highly efficacious against invasive disease[4] and somewhat efficacious against otitis media[4,5] and pneumonia.[6] Conjugate vaccines reduce nasopharyngeal carriage of vaccine-type strains but often increase the frequency of carriage of non–vaccine-type strains.[7-12]

The efficacy of the vaccine in infants given fewer than four doses or in older children is unknown. Because the vaccine does not include most of the 90 pneumococcal serotypes, an increase in disease caused by serotypes not included in the vaccine or not related to those in the vaccine is possible; this effect was seen during a clinical trial evaluating its efficacy against otitis media.[5] Whether vaccination of young children will reduce carriage and subsequently affect disease in other age groups is unclear. To evaluate these questions, we examined data from the Active Bacterial Core Surveillance of the Centers for Disease Control and Prevention (CDC).

METHODS

The Active Bacterial Core Surveillance, which is part of the Emerging Infections Program Network of the CDC, is an active, population-based, laboratory-based surveillance system. Between January 1, 1996, and December 31, 2001, the Active Bacterial Core Surveillance continuously monitored invasive pneumococcal infections in Portland, Oregon (three counties); San Francisco County, California; Minneapolis and St. Paul, Minnesota (seven counties); the Baltimore metropolitan area in Maryland (six counties); the state of Connecticut; and the Atlanta, Georgia, metropolitan area (eight counties). In 1998, the Atlanta site was expanded to include 12 additional counties, and surveillance began in Rochester, New York (7 counties). The total population under surveillance in 2000 was 16.0 million persons, including 433,591 children under two years of age and 652,551 children from two through four years of age.

A case of invasive pneumococcal disease was defined by the isolation of *Streptococcus pneumoniae* from a sample of normally sterile body fluid taken from a surveillance-area resident. To identify cases, surveillance personnel periodically contacted all clinical microbiology laboratories in their areas and conducted audits of laboratory records at least every six months to ensure complete reporting. Data on patients were collected with the use of a standardized questionnaire that elicited information on demographic features, clinical syndromes, and disease outcomes. Data on human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) were collected in five sites (all except Georgia and New York State). The addition of the New York site and the expansion of the Georgia site, both beginning in January 1998, were the only changes made to the Active Bacterial Core Surveillance between 1996 and 2001; no changes were made in methods of data collection.

Pneumococcal isolates were sent to reference laboratories for serotyping by the quellung reaction. Isolates from Minnesota were tested at the Minnesota Department of Health, and all others were tested at the CDC. Vaccine-type strains included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. We defined vaccine-related strains as pneumococci with serotypes within the same serogroup as the vaccine types (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B). All other serotypes were considered nonvaccine types. Serotypes in the 23-valent polysaccharide vaccine but not in the conjugate vaccine included 1, 2, 3, 5, 7F, 8, 10A, 11A, 12F, 15B, 20, 22F, and 33F.

Susceptibility testing of isolates was performed with the use of broth microdilution[13] at the CDC, the Minnesota Department of Health, or the University of Texas Health Science Center at San Antonio. Isolates were defined as susceptible, of intermediate susceptibility, or resistant according to the 2002 definitions of the National Committee for Clinical Laboratory Standards.[13] Isolates with intermediate susceptibility and resistant isolates were classified as nonsusceptible. Strains that were nonsusceptible to three or more drug classes were considered to be multiply resistant.

Annual cumulative incidence rates were calculat-

ed for 1996 through 1999 on the basis of population estimates from the U.S. Census Bureau for those years; the rates for 2000 and 2001 were calculated from 2000 Census data. To calculate serotype-specific disease rates, we assumed that the distribution of serotypes for cases with missing serotype data (11.7 percent of cases) was the same as the distribution for cases with serotype information available. The same method was used to impute missing data on race (11.0 percent) and hospitalization (0.2 percent). To verify the results, the analyses of rates were repeated with only cases with complete data included. The rates are reported as cases per 100,000 population.

To assess changes in disease rates after the introduction of vaccination, we calculated the numbers of cases and noncases in the surveillance population, using Active Bacterial Core Surveillance data and U.S. Census figures. We then used the chi-square test or Fisher's exact test to compare the proportion of the population who had invasive disease in the years following the introduction of vaccination (2000 or 2001) with a base-line rate (either the average rate for 1998 and 1999 combined or the rate for 1999 alone). We calculated Pearson's correlation coefficients to match the changes in disease rates among adults to those among children. Statistical analyses were conducted with SAS, version 8.0, and Epi Info, version 6.0,[14] software. We calculated 95 percent confidence intervals, and two-sided P values that were less than 0.05 were considered to indicate statistical significance.

RESULTS

During the period from 1998 through 2001, a total of 13,568 cases of invasive pneumococcal disease were identified; isolates were available for 11,992 (88 percent). The rates of invasive disease in 1998, 1999, 2000, and 2001 were 24.2, 24.4, 21.2, and 17.3 cases per 100,000 persons, respectively. The average for the base-line period of 1998 and 1999 was 24.3 per 100,000.

CHILDREN UNDER FIVE YEARS OF AGE

From 1998 through 2001, 3285 cases of invasive pneumococcal disease were identified in children under five years of age. The rate declined by 59 percent (95 percent confidence interval, 54 to 63 percent), from an average of 96.4 cases per 100,000 in 1998 and 1999 to 39.7 per 100,000 in 2001. Significant declines in disease rates occurred among children two years old or less (59.0 cases per 100,000 in 2001, as compared with 188.0 per 100,000 in 1998 and 1999) (Fig. 1). As compared with the base-line values for 1998 and 1999 combined, the rates of disease in 2000 were 17 percent lower among children under 12 months old (139.3 cases per 100,000 vs. 168.1; 95 percent confidence interval, 5 to 28 percent) and 27 percent lower among children 12 to 23 months old (152.7 cases per 100,000 vs. 208.2; 95 percent confidence interval, 17 to 35 percent); by 2001, the disease rates were 69 percent lower (52.3 cases per 100,000 vs. 168.1; 95 percent confidence interval, 62 to 75 percent) and 68 percent lower (65.8 vs. 208.2; 95 percent confidence interval, 62 to 74 percent), respectively, in these age groups ($P<0.001$ for all comparisons). In children 24 to 35 months old, the rate was 44 percent lower in 2001 than in 1998 and 1999 (35.6 cases per 100,000 vs. 63.3; 95 percent confidence interval, 27 to 56 percent). For children who were three or four years of age, the rates in 2001 were not significantly different from the base-line values.

Among children under two years of age, the magnitude of the decline from 1998 and 1999 to 2001 was substantially larger for black children

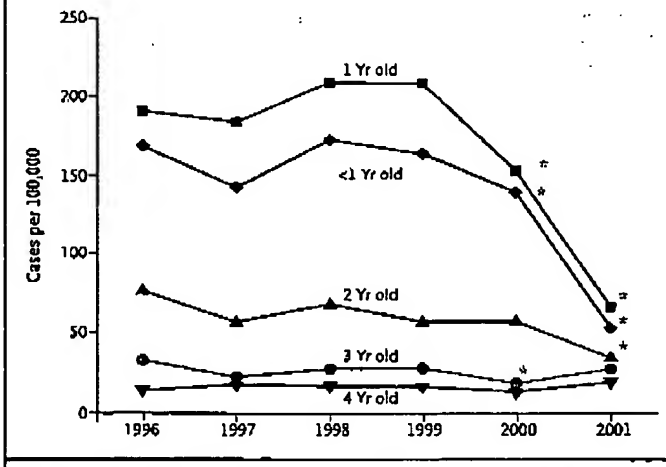

Figure 1. Rates of Invasive Pneumococcal Disease among Children under Five Years Old, According to Age and Year.

Data are from the Active Bacterial Core Surveillance from 1996 through 2001. The 1996 and 1997 rates do not include data from New York State. Asterisks indicate $P<0.05$ for comparisons of the rate in 2000 or 2001 with the combined rate for 1998 and 1999.

(from 437.6 cases per 100,000 to 119.6) than for white children (from 132.7 to 50.6). However, the percent changes were similar: a 73 percent decline among blacks (95 percent confidence interval, 66 to 78 percent) and a 62 percent decline among whites (95 percent confidence interval, 55 to 68 percent). The percent change in the rate of disease requiring hospitalization (from 56.8 cases per 100,000 to 21.2, a decline of 63 percent) among children under two years of age was not significantly different from the percent change in the rate of disease treated without hospitalization (from 132.7 to 38.1, a decline of 71 percent). Likewise, the percent change in the rate of pneumococcal meningitis (from 10.3 cases per 100,000 to 4.2, a decline of 59 percent) was similar to that for the rate of other syndromes (from 179.4 to 55.8, a decline of 69 percent). The percent change in the rate of disease was largest in California, with a decline of 85 percent (95 percent confidence interval, 37 to 96 percent), and New York State, with a decline of 83 percent (95 percent confidence interval, 67 to 92 percent), and smallest in Oregon, with a decline of 38 percent (95 percent confidence interval, 2 to 61 percent) (Fig. 2).

For children under two years of age, the rate of disease due to vaccine serotypes declined by 78 percent overall; significant declines in disease were seen for all individual serotypes included in the vaccine (Table 1). As compared with base line, the rate of disease due to vaccine-related strains as a group was 50 percent lower in 2001. The rate of disease due to nonvaccine serotypes was 27 percent higher in 2001, but this change was not statistically significant.

PERSONS FIVE YEARS OF AGE OR OLDER

Disease rates also fell among persons for whom the vaccine is not recommended (Fig. 3). Although

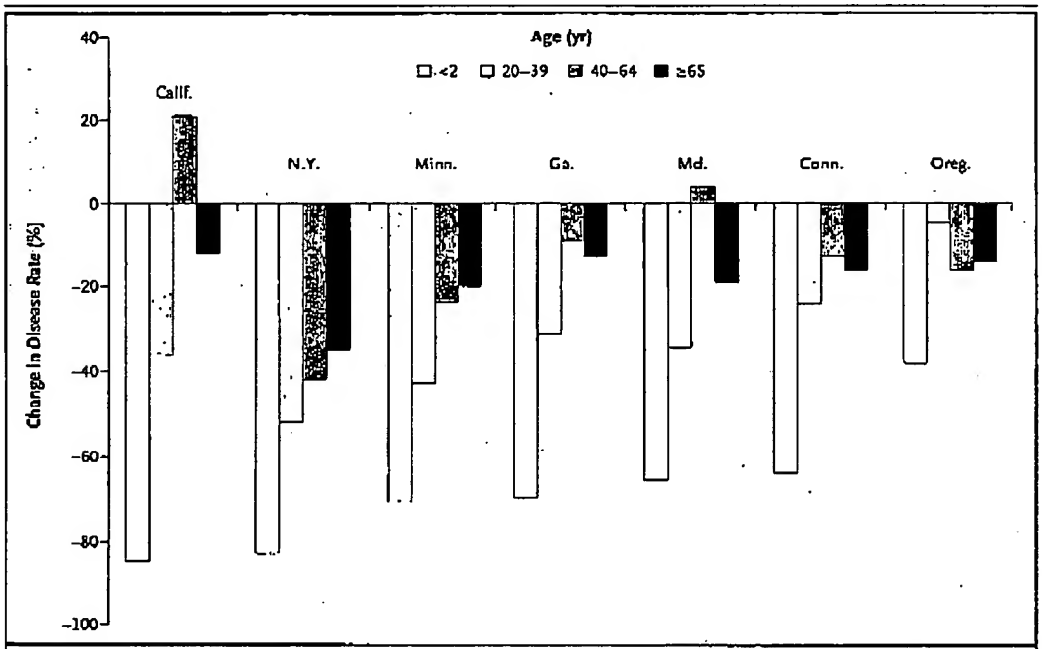

Figure 2. Percent Changes in the Rates of Invasive Pneumococcal Disease, According to Age Group and the State in Which the Active Bacterial Core Surveillance Site Was Located.

The percent decline was calculated by comparing the incidence in 2001 with the average incidence in 1998 and 1999. Within states, the decline among children under 2 years old correlated significantly with the decline among persons 20 to 39 years of age ($r=0.89$, $P=0.008$), but not with the decline among persons 40 to 64 years of age ($r=-0.09$, $P=0.85$) or 65 years or older ($r=0.36$, $P=0.42$).

Table 1. Changes in Estimated Rates of Invasive Pneumococcal Disease among Children under Two Years of Age, According to Year and Serotype, from 1998 through 2001.*

Serotype	Average for 1998 and 1999		2001		% Change in Estimated Rate (95% CI)‡	P Value§
	No. of Cases	Estimated Rate†	No. of Cases	Estimated Rate†		
		cases/100,000		*cases/100,000*		
All vaccine serotypes	563.5	156.1	124	33.6	−78 (−82 to −74)	<0.001
4	52	14.4	9	2.4	−83 (−91 to −67)	<0.001
6B	75	20.8	27	7.3	−65 (−76 to −48)	<0.001
9V	31.5	8.7	12	3.3	−63 (−79 to −35)	<0.001
14	228.5	63.3	39	10.6	−83 (−88 to −77)	<0.001
18C	51.5	14.3	12	3.3	−77 (−87 to −61)	<0.001
19F	78.5	21.8	14	3.8	−83 (−90 to −72)	<0.001
23F	46.5	12.9	11	3.0	−77 (−87 to −59)	<0.001
All vaccine-related serotypes¶	70.5	19.6	36	9.8	−50 (−65 to −31)	<0.001
6A	32	8.9	18	4.9	−45 (−66 to −12)	0.02
9A	10.5	2.9	3	0.8	−72 (−89 to −11)	0.04
19A	20	5.5	12	3.3	−40 (−68 to +5)	0.09
All nonvaccine serotypes	44.5	12.4	58	15.7	+27 (−6 to +73)	0.14
1	2.5	0.7	1	0.3	−57 (−96 to +169)	0.43
3	2.5	0.7	4	1.1	+57 (−51 to +431)	0.53
5	0	0	1	0.3	Not defined	0.34
7F	5.5	1.5	6	1.6	+7 (−58 to +163)	0.89
12F	6.5	1.8	7	1.9	+6 (−56 to +145)	0.89

* The data are from the Active Bacterial Core Surveillance.
† The estimated rates were calculated on the assumption that the serotype distribution for cases with missing serotype data (12 percent of all cases) was the same as the distribution for cases with serotype data available.
‡ CI denotes confidence interval.
§ The P value was calculated by a chi-square test or Fisher's exact test that compared the estimated number of cases and noncases (the total surveillance population minus the number of estimated cases) in 2001 with the same figures for 1998 and 1999 combined. The estimated number of cases and totals were calculated on the assumption that the serotype distribution for cases with missing serotype data was the same as the distribution for cases with serotype data available. Repeated analysis with only cases with known serotypes included rather than the estimated number of cases did not change the results.
¶ Types 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B are included.

no significant change was observed among persons 5 through 19 years of age, the rate of disease among persons 20 through 39 years of age was 21 percent lower in 2000 than at base line in 1998 and 1999 (8.9 cases per 100,000 vs. 11.2; 95 percent confidence interval, 11 to 29 percent) and 32 percent lower in 2001 (7.6 vs. 11.2; 95 percent confidence interval, 23 to 39 percent; P<0.001). The rates were significantly lower both for disease caused by vaccine serotypes and for disease caused by nonvaccine serotypes, although the decline was larger for the former (Table 2). Significant declines were noted in disease caused by some individual serotypes included in the vaccine, particularly 4, 9V, 14, and 19F. Within surveillance sites, the size of the decline among persons 20 to 39 years of age correlated with the size of the decline among children under 2 years old (r=0.89, P=0.008) (Fig. 2). In sites

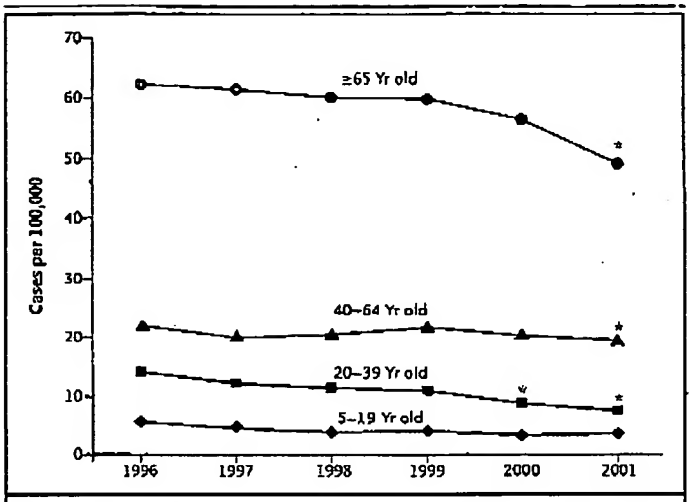

Figure 3. Rates of Invasive Pneumococcal Disease among Persons at Least Five Years Old, According to Age Group and Year.

Data are from the Active Bacterial Core Surveillance from 1996 through 2001. The 1996 and 1997 rates do not include data from New York State. Asterisks indicate P<0.05 for comparisons of the rate in 2000 or 2001 with the combined rate for 1998 and 1999.

where information on HIV infection and AIDS was recorded, the number of cases in persons without known HIV infection or AIDS dropped by 38 percent, from 270.5 in 1998 and 1999 to 168.0 in 2001; there was no significant change in the number of cases in persons with HIV or AIDS (an average of 81 cases in 1998 and 1999 and 82 cases in 2001).

Among persons 40 to 64 years of age, the overall rate of disease was 8 percent lower in 2001 than in 1998 and 1999 (19.7 cases per 100,000 vs. 21.5; 95 percent confidence interval, 1 to 15 percent; P=0.03) (Fig. 3). The change in the overall rate of disease in this age group was primarily due to a decline in the rate of disease caused by serotypes included in the vaccine (Table 2). Among the individual serotypes included in the vaccine, only the change in the rate of disease due to serotype 14 was statistically significant.

Among persons 65 years of age or older, the rate of disease was 18 percent lower in 2001 than at base line (49.5 cases per 100,000 vs. 60.1; 95 percent confidence interval, 11 to 24 percent; P<0.001) (Fig. 3). The rates were lower for disease caused by vaccine serotypes and vaccine-related serotypes; significant declines were seen for disease caused by vaccine serotypes 4, 9V, 14, and 23F (Table 2). The rate of disease caused by serotypes included in the 23-valent polysaccharide vaccine and not in the conjugate vaccine was the same in 2001 as in 1998 and 1999 (11.9 cases per 100,000).

Among nonvaccine serotypes, the rate of serotype 1 disease was lower in some adult age groups in 2001 than in 1998 and 1999: for those between 40 and 64 years old, the rate declined from 0.5 to 0.1 case per 100,000 (P<0.001), and for those 65 years of age or older, the rate declined from 0.7 to 0.3 (P=0.05). The rate of serotype 5 disease was higher in 2001 than in 1998 and 1999 among persons 20 to 39 years old and those 40 to 64 years old, but this change was attributable to an increase in the number of cases caused by serotype 5 in one surveillance site (California), which had 1 isolate in 1998 and 1999 and 14 isolates in 2001.

DRUG-RESISTANT INVASIVE DISEASE

The proportion of isolates that were not susceptible to penicillin decreased slightly between 1999 (861 of 3355, 26 percent) and 2001 (589 of 2495, 24 percent; P=0.08). In 1999, 11 percent of isolates were of intermediate susceptibility to penicillin and 15 percent were resistant; in 2001, 10 percent were of intermediate susceptibility and 14 percent were resistant. Between 1999 and 2001, the change in the rate of disease caused by strains that were not susceptible to penicillin (from 6.3 to 4.1, a decline of 35 percent; 95 percent confidence interval, 28 to 41 percent; P<0.001) did not differ significantly from the change in the rate of disease caused by penicillin-susceptible strains (from 18.1 to 13.1, a decline of 28 percent; 95 percent confidence interval, 23 to 31 percent).

Among children under two years of age, the proportion of isolates not susceptible to penicillin was 38 percent in 1999 (258 of 684) and 35 percent in 2001 (77 of 218) (P=0.58); the rate of disease caused by penicillin-nonsusceptible and penicillin-susceptible strains fell by 70 percent (from 70.0 to 20.9; 95 percent confidence interval, 62 to 77 percent) and 67 percent (from 115.5 to 38.5; 95 percent confidence interval, 60 to 72 percent), respectively. The rate of disease due to penicillin-nonsusceptible strains also declined significantly among persons 65 years of age or older (from 16.7 to 12.6, a decline of 25 percent; 95 percent con-

fidence interval, 9 to 36 percent). The percent changes in the rate of disease caused by erythromycin-resistant and multidrug-resistant strains were similar to those in the rate of disease caused by penicillin-resistant strains.

DISCUSSION

The use of the pneumococcal conjugate vaccine has reduced the burden of invasive disease in young children, for whom the vaccine is indicated, and may be preventing disease in adults. In 2001, the rate of invasive disease among children under two years of age was 69 percent lower than in 1998 and 1999. Declines in disease rates also were evident among adults (a decline of 32 percent for those 20 to 39 years old, 8 percent for those 40 to 64 years old, and 18 percent for those 65 years old or older). Our data confirm that the change in disease rates reported among children who were members of Northern California Kaiser Permanente[15] is occurring in the United States as a whole and suggest that unvaccinated adults are benefiting from the use of the vaccine in children. In addition, the vaccine is preventing a substantial proportion of the disease caused by drug-resistant strains and is providing some protection against disease caused by vaccine-related serotypes, as was seen in a clinical trial evaluating its efficacy against otitis media.[5]

Although the largest drop in disease rates occurred among children under two years of age, a significant decline also occurred among two-year-olds (43.8 percent). No significant change was seen among older children. These findings are consistent with recommendations for the use of vaccine[1,2] and reported patterns of vaccine use[3]; data on vaccine coverage are not yet available. The manufacturer sold 9 million doses in 2000 and 15.5 million doses in 2001; less than 10 percent of private-sector sales were for children two years old or more (Paradiso P, Wyeth Lederle Vaccines: personal communication). Approximately 4 million children are born in the United States annually; therefore, 32 million doses would have been required to provide the 4-dose infant series for children born in 2000 and 2001, and millions more would have been needed for catch-up vaccination of children under two years of age and those from two through four years of age who had conditions that put them at high risk for pneumococcal infection. Although they are estimates, these figures suggest that changes in disease rates are occurring even though children are not fully vaccinated; the vaccine may provide protection with less than the full number of recommended doses and through decreased transmission of pneumococci between children.

The reduction in disease burden seen among adults is noteworthy. Although young children have the highest risk of invasive disease, most cases of pneumococcal disease and nearly all deaths from pneumococcal disease occur in adults.[16] Much of the change we observed in adults may be due to decreased transmission of pneumococci from children. Children are a reservoir for pneumococci; contact with young children in the household is a risk factor for invasive disease in adults,[17,18] and the frequency of nasopharyngeal carriage is higher in adults with young children than in other adults.[19] Conjugate vaccines have been shown to reduce the carriage of vaccine-type strains in vaccinated children,[7-12] thus reducing opportunities for transmission.

Multidrug-resistant pneumococci are a worldwide problem. In response, programs have been developed to reduce antimicrobial use.[20,21] Our data indicate that conjugate vaccine is another effective tool for preventing infections caused by drug-resistant strains; 35 percent fewer infections due to penicillin-nonsusceptible strains occurred in 2001 than in 1999. Resistance is closely linked to pneumococcal serotype; in 1998, three fourths of penicillin-nonsusceptible pneumococci were of serotypes that were included in the vaccine, although pneumococci of common serotypes that were included in the vaccine, such as 4 and 18C, were rarely drug-resistant.[22] Because the vaccine prevented a similar amount of disease caused by penicillin-susceptible and penicillin-nonsusceptible strains, the proportion of pneumococci with decreased susceptibility to penicillin did not change substantially.

We cannot determine to what extent the observed changes are due to the introduction of vaccination or to other factors. Certain findings, such as the significant decline in non–vaccine-type disease in adults 20 to 39 years of age, suggest that secular trends may explain some of the observations. However, we found no change in the rate of disease caused by pneumococci with serotypes unique to the polysaccharide vaccine or in the number of cases in persons with HIV infection, results suggesting that the increasing use of polysaccharide vaccine and highly active antiretroviral therapy does

Table 2. Changes in Estimated Rates of Invasive Pneumococcal Disease among Adults, According to Age Group, Year, and Serotype, from 1998 through 2001.*

Age and Serotype	Average for 1998 and 1999		2001		% Change in Estimated Rate (95% CI)‡	P Value§
	No. of Cases	Estimated Rate†	No. of Cases	Estimated Rate†		
		cases/100,000		*cases/100,000*		
20–39 Yr						
All vaccine serotypes	285.5	6.60	176	3.97	−40 (−49 to −29)	<0.001
4	86.5	2.00	50	1.13	−44 (−58 to −23)	<0.001
6B	19	0.44	18	0.41	−8 (−46 to +56)	0.74
9V	51.5	1.19	27	0.61	−49 (−66 to −24)	0.001
14	62	1.43	38	0.86	−40 (−58 to −16)	0.003
18C	19	0.44	12	0.27	−39 (−68 to +11)	0.13
19F	18.5	0.43	9	0.20	−53 (−76 to −4)	0.05
23F	29	0.67	22	0.50	−25 (−54 to +17)	0.23
All vaccine-related serotypes¶	60	1.39	48	1.08	−22 (−44 to +7)	0.14
All nonvaccine serotypes	138.5	3.21	114	2.57	−20 (−35 to −1)	0.04
40–64 Yr						
All vaccine serotypes	481.5	11.58	431	9.95	−14 (−23 to −4)	0.006
4	113.5	2.73	118	2.72	−1 (−19 to +23)	0.99
6B	54	1.30	44	1.02	−22 (−44 to +9)	0.17
9V	74.5	1.79	64	1.48	−17 (−38 to +8)	0.18
14	108.5	2.61	76	1.75	−33 (−48 to −14)	0.002
18C	28.5	0.69	40	0.92	+33 (−8 to +97)	0.16
19F	38	0.91	32	0.74	−19 (−45 to +19)	0.32
23F	64.5	1.55	57	1.32	−15 (−36 to +15)	0.29
All vaccine-related serotypes¶	103.5	2.49	103	2.38	−4 (−23 to +20)	0.74
All nonvaccine serotypes	310	7.46	321	7.41	−1 (−13 to +13)	0.93

not explain our findings. The percent change in the rate of disease among children was similar for hospitalized patients and outpatients and for pneumococcal meningitis and other syndromes, suggesting that changes in culturing practices did not explain the observed decline.

Preventing pneumococcal disease is a priority for the United States. The Healthy People 2010 objectives include decreasing the incidence of invasive pneumococcal infections to 46 cases per 100,000 persons under 5 years of age and to 42 per 100,000 persons 65 years of age or older.[23] The target for children has been met, and we are closer to the goal for adults. More data are also needed to determine how far disease rates will fall as vaccine coverage increases and to assess the effect of the vaccine on pneumonia and other noninvasive syndromes. Whether vaccine use will slow the emergence of resistant pneumococci and whether disease due to pneumococci with nonvaccine serotypes will become more common are questions that do not yet have definitive answers. Although questions remain, our data indicate that the pneumococcal conjugate vaccine is working well in the U.S. population.

Table 2. (Continued.)

Age and Serotype	Average for 1998 and 1999		2001		% Change in Estimated Rate (95% CI)‡	P Value§
	No. of Cases	Estimated Rate†	No. of Cases	Estimated Rate†		
		cases/100,000		*cases/100,000*		
≥65 Yr						
All vaccine serotypes	511.5	33.43	374	23.91	−29 (−36 to −20)	<0.001
4	76.5	5.00	58	3.71	−26 (−44 to −1)	0.05
6B	66	4.31	57	3.64	−16 (−37 to +13)	0.28
9V	77.5	5.10	51	3.26	−36 (−52 to −13)	0.005
14	144	9.41	94	6.01	−36 (−48 to −20)	<0.001
18C	27	1.76	19	1.21	−31 (−58 to +12)	0.17
19F	34.5	2.25	34	2.17	−4 (−34 to +43)	0.95
23F	86	5.62	61	3.90	−31 (−47 to −9)	0.01
All vaccine-related serotypes¶	128.5	8.38	102	6.52	−22 (−38 to −4)	0.02
All nonvaccine serotypes	278	18.18	298	19.05	+5 (−8 to +20)	0.52

* The data are from the Active Bacterial Core Surveillance.

† The estimated rates were calculated on the assumption that the serotype distribution for cases with missing serotype data (12 percent of all cases) was the same as the distribution for cases with serotype data available.

‡ CI denotes confidence interval.

§ The P value was calculated by a chi-square test or Fisher's exact test that compared the estimated number of cases and noncases (the total surveillance population minus the number of estimated cases) in 2001 with the same figures for 1998 and 1999 combined. The estimated number of cases was calculated on the assumption that the serotype distribution for cases with missing serotype data was the same as the distribution for cases with serotype data available. Repeated analysis with only cases with known serotypes included rather than the estimated number of cases did not change the results.

¶ Types 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B are included.

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